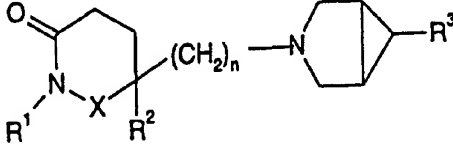
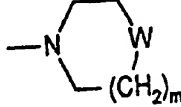


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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/EP96/05000 (22) International Filing Date: 11 November 1996 (11.11.96) (30) Priority Data: 9524157.6 25 November 1995 (25.11.95) GB (71) Applicant (for GB only): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (71) Applicant (for JP only): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (71) Applicant (for all designated States except GB JP US): PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V./S.A. (BE/IE); La Touche House, International Financial Services Centre, Dublin 1 (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): MACKENZIE, Alexander, Roderick [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MARCHINGTON, Allan, Patrick [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MIDDLETON, Donald, Stuart [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MEADOWS,</p>		<p>Sandra, Dora [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (74) Agents: MOORE, James, W. et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). (81) Designated States: CA, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.</p>
<p>(54) Title: 5-AZABICYCLO(3.1.0)HEXYLALKYL-2-PIPERIDONES AND -GLUTARIMIDES AS NEUROKININ RECEPTOR ANTAGONISTS</p> <p>(57) Abstract</p> <p>Compounds of formula (I) and salts thereof, wherein: R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, aryl or aryl(C<sub>1</sub>-C<sub>4</sub>)alkyl; wherein the C<sub>1</sub>-C<sub>6</sub> alkyl group is optionally substituted by fluorine and the C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkyl group is optionally substituted in the cycloalkyl ring by up to two substituents each independently selected from halo, C<sub>1</sub>-C<sub>4</sub> alkoxy or halo(C<sub>1</sub>-C<sub>4</sub>)alkoxy; R<sup>2</sup> is phenyl optionally substituted with one or two halo substituents or is indolyl, thienyl, benzothienyl or naphthyl; R<sup>3</sup> is NH<sub>2</sub>, -NR<sup>4</sup>SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -NR<sup>4</sup>SO<sub>2</sub> aryl, -NR<sup>4</sup>SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>, -NR<sup>4</sup>CO(C<sub>1</sub>-C<sub>6</sub> alkyl), -NR<sup>4</sup>CO aryl or a group or formula (a) wherein W is O, NR<sup>5</sup>, CH(OH), CHCO<sub>2</sub>H, CHN(R<sup>4</sup>)<sub>2</sub>, CHF, CF<sub>2</sub>, C=O or CH<sub>2</sub>; R<sup>4</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sup>5</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>4</sub>-C<sub>8</sub> cycloalkanoyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>2</sub>-C<sub>6</sub>)alkanoyl, aryl CO-, C<sub>1</sub>-C<sub>6</sub> alkyl SO<sub>2</sub>-, (R<sup>4</sup>)<sub>2</sub>NSO<sub>2</sub>-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl SO<sub>2</sub>-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl-SO<sub>2</sub>- or aryl SO<sub>2</sub>-, X is CH<sub>2</sub> or C=O; m is 0, 1 or 2 with the proviso that m is not 0 when W is NR<sup>5</sup>, C=O, or O; and n is an integer of from 1 to 4, are neurokinin receptor antagonists of utility in the treatment of a variety of medical conditions including urinary incontinence, asthma and related conditions.</p> <div style="text-align: center;">  <p>(I)</p>  <p>(a)</p> </div>		

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**5-AZABICYCLO(3.1.0)HEXYLALKYL-2-PIPERIDONES AND -GLUTARIMIDES AS NEUROKININ RECEPTOR ANTAGONISTS**

This invention relates to piperidone derivatives which are neurokinin receptor  
5 antagonists of utility in the treatment of a variety of medical conditions including,  
for example, urinary incontinence, asthma and related conditions. More  
particularly this invention relates to certain 5-aryl-5-(azabicyclo[3.1.0]hexane  
alkyl)-N-substituted-piperidone derivatives, to processes for their preparation,  
compositions thereof and their use in medicine.

10 According to the specification of our co-pending International patent  
application WO 96/05193 we describe and claim a series of 5-aryl-5-  
azetidinyllalkyl-piperidone derivatives. The compounds are antagonists of  
tachykinins, including neurokinin A, neurokinin B and Substance P, acting at the  
human neurokinin-1 (NK<sub>1</sub>), neurokinin-2 (NK<sub>2</sub>) or neurokinin-3 (NK<sub>3</sub>) receptor, and  
15 are therefore potentially useful for preventing or treating a variety of medical  
conditions in which these receptors have been implicated, including inflammatory  
diseases such as arthritis, psoriasis, asthma or inflammatory bowel disease;  
central nervous system disorders such as anxiety, depression, dementia or  
psychosis; gastro-intestinal disorders such as functional bowel disease, irritable  
20 bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis, Crohn's  
disease or diseases caused by Helicobacter pylori or other bacteria; urogenital  
tract disorders such as incontinence, hyperreflexia, impotence or cystitis;  
pulmonary disorders such as chronic obstructive airways disease; allergies such  
as eczma, contact dermatitis, atopic dermatitis, urticaria, rhinitis or  
25 hypersensitivity disorders such as to poison ivy; vasospastic diseases such as  
angina or Reynaud's disease; proliferative disorders such as cancer or a disorder  
involving fibroblast proliferation; fibrosing or collagen diseases such as  
scleroderma or eosinophilic fascioliasis; reflux sympathetic dystrophy such as  
shoulder/hand syndrome; addiction disorders such as alcoholism; stress-related  
30 somatic disorders; peripheral neuropathies such as diabetic neuropathy,  
neuralgia, causalgia, painful neuropathy, burns, herpetic neuralgia or post herpetic  
neuralgia; neuropathological disorders such as Alzheimer's disease or

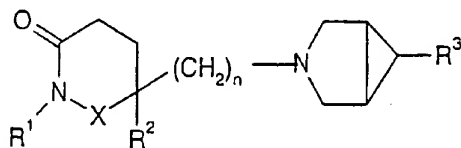
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multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus; rheumatic diseases such as fibrositis or emesis; opthalmic diseases such as retinopathy; viral diseases such as colds and  
 5 influenza; cough; acute or chronic pain or migraine.

The present invention provides a further series of related compounds wherein the piperidone-5-substituent is an azabicyclo [3.1.0]hexanealkyl-group. Also claimed are the corresponding di-one (glutarimide) derivatives. The compounds are potent and selective antagonists of tachykinins including  
 10 neurokinin A, neurokinin B and substance P, active at the human NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> receptors and they thus have potential utility in any of the disease states indicated above including, in particular treating or preventing inflammatory diseases such as arthritis, psoriasis, asthma or inflammatory bowel disease; central nervous system disorders such as anxiety, depression, dementia or  
 15 psychosis; gastro-intestinal disorders such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease; urogenital tract disorders such as incontinence or cystitis; pulmonary disorders such as chronic obstructive airways disease; allergies such as eczema, contact dermatitis or rhinitis; hypersensitivity disorders such as to poison ivy;  
 20 peripheral neuropathies such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, burns, herpetic neuralgia or post-herpetic neuralgia; cough or acute or chronic pain.

Thus, the present invention provides compounds having the formula:

25



30

(I)

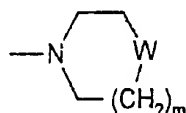
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and pharmaceutically acceptable salts thereof, wherein:

$R^1$  is  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_7$  cycloalkyl,  $C_3$ - $C_7$  cycloalkyl( $C_1$ - $C_4$ )alkyl, aryl or aryl-  
 5 ( $C_1$ - $C_4$ )alkyl; wherein the  $C_1$ - $C_6$  alkyl group is optionally substituted by one or more  
 fluorine atoms and the  $C_3$ - $C_7$  cycloalkyl or  $C_3$ - $C_7$  cycloalkyl( $C_1$ - $C_4$ )alkyl group is  
 optionally substituted in the cycloalkyl ring by up to two substituents each  
 independently selected from halo,  $C_1$ - $C_4$  alkoxy or halo( $C_1$ - $C_4$ )alkoxy;

$R^2$  is phenyl optionally substituted with one or two halo substituents or is  
 indolyl, thienyl, benzothienyl or naphthyl;

10  $R^3$  is  $NH_2$ ,  $-NR^4 SO_2(C_1$ - $C_6$  alkyl),  $-NR^4 SO_2$  aryl,  $-NR^4 SO_2 N(R^4)_2$ ,  
 $-NR^4 CO(C_1$ - $C_6$  alkyl),  $-NR^4 CO$  aryl or a group of the formula:



15

wherein W is O,  $NR^5$ ,  $CH(OH)$ ,  $CHCO_2H$ ,  $CHN(R^4)_2$ ,  $CHF$ ,  $CF_2$ ,  $C=O$  or  $CH_2$ ;

$R^4$  is H or  $C_1$ - $C_6$  alkyl;

$R^5$  is H,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_7$  cycloalkyl,  $C_3$ - $C_7$  cycloalkyl( $C_1$ - $C_6$ )alkyl,  $C_2$ - $C_6$   
 alkanoyl,  $C_4$ - $C_8$  cycloalkanoyl,  $C_3$ - $C_7$  cycloalkyl( $C_2$ - $C_6$ )alkanoyl, aryl  $CO$ -,  
 20  $C_1$ - $C_6$  alkyl  $SO_2$ -,  $(R^4)_2 NSO_2$ -,  $C_3$ - $C_7$  cycloalkyl  $SO_2$ -,  $C_3$ - $C_7$  cycloalkyl-  
 ( $C_1$ - $C_6$ )alkyl  $SO_2$ - or aryl  $SO_2$ -;

X is  $CH_2$  or  $C=O$ ;

m is 0, 1 or 2 with the proviso that m is not 0 when W is  $NR^5$ ,  $C=O$ , or O;  
 and n is an integer of from 1 to 4.

25

In the above definitions of  $R^1$ ,  $R^3$  and  $R^5$ , aryl means phenyl optionally  
 substituted by halo,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, halo( $C_1$ - $C_4$ )alkyl or  
 halo( $C_1$ - $C_4$ )alkoxy, and halo means fluoro, chloro, bromo or iodo. Alkyl and  
 alkoxy groups containing three or more carbon atoms may be straight or  
 30 branched-chain.

The pharmaceutically acceptable salts of the compounds of the formula (I)  
 include the acid addition and the base salts thereof. Suitable acid addition salts  
 are formed from acids which form non-toxic salts; examples are the hydrochloride,

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hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Suitable base salts are formed from bases which form non-toxic salts; examples are the aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

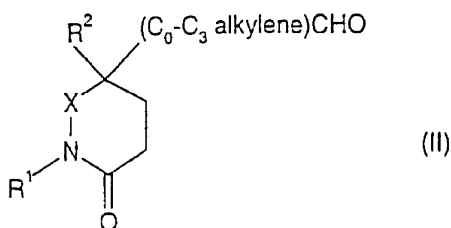
The compounds of the formula (I) may contain one or more asymmetric carbon atoms and may therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and mixtures thereof. Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation or chromatography of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof.

Preferred examples of the compounds of the formula (I) are those wherein X is CH<sub>2</sub>, R<sup>1</sup> is cyclopropylmethyl or benzyl; R<sup>2</sup> is 3,4-dichlorophenyl, n is 2 and R<sup>3</sup> is morpholino, methanesulphonylamino, pentafluorophenylsulphonyl, fluorophenylsulphonyl, or fluorophenylcarboxamido.

The preferred compounds of the formula (I) and salts thereof where n is 2 have the (S)-stereochemistry at the position of attachment of the alkylene and R<sup>2</sup> groups to the pyridone ring.

Particular and preferred examples of compounds of the invention include: 5(S)-5-(3,4-dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,6-morpholino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone.

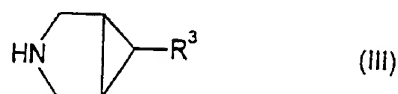
The compounds of the formula (I) provided by this invention can be prepared by reductive amination using as starting materials a compound of the formula:-



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where  $R^1$ ,  $R^2$  and X are as previously defined for a compound of the formula (I),  
and a compound of the formula:-

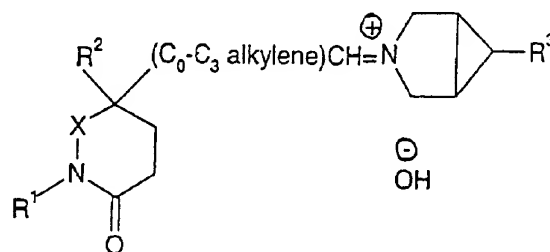
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or an acid addition salt thereof, where  $R^3$  is as previously defined for a compound  
of the formula (I). The reaction is preferably carried out in the presence of a  
suitable acid, e.g. acetic acid.

The reaction proceeds via the initial formation of an intermediate iminium salt  
of the formula:

15



20

(IIIA)

which may be stable and isolatable. The reaction is preferably carried out without  
isolation of the intermediate of the formula (IIIA) in which case it is reduced in situ  
to provide a compound of formula (I).

In a typical procedure, an aldehyde of the formula (II) is first reacted with a  
compound of the formula (III) in a suitable solvent, e.g. tetrahydrofuran, and the  
mixture then treated with a suitable reducing agent, e.g. sodium triacetoxy-  
borohydride or sodium cyanoborohydride, in the presence of a suitable acid, e.g.

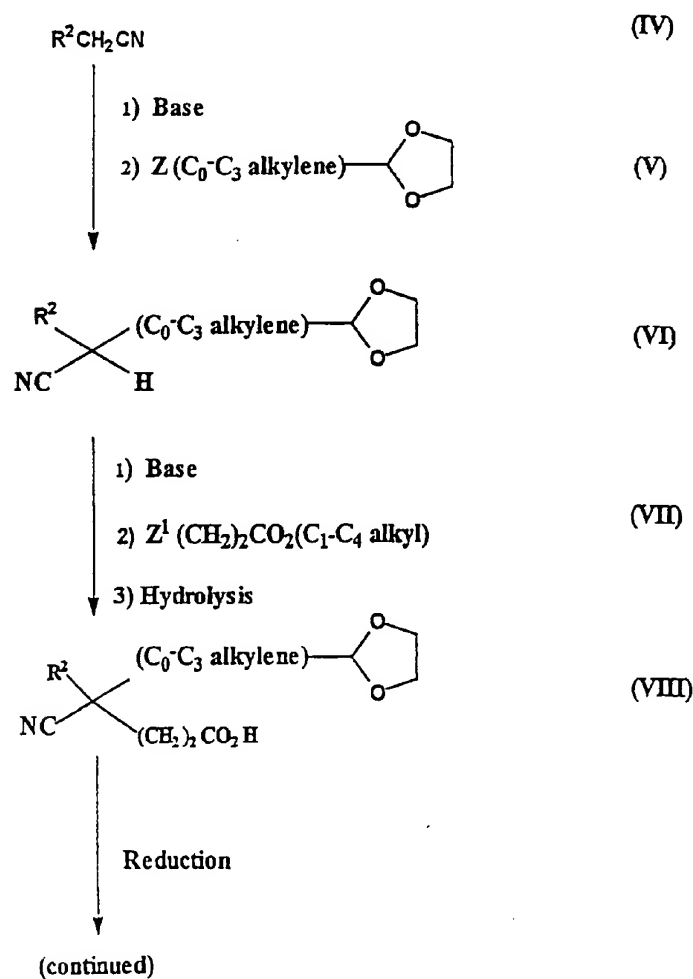
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acetic acid, to give the required product. If an acid addition salt of a compound of the formula (III) is used as a starting material, a suitable acid acceptor, e.g. triethylamine, can be added prior to the addition of the reducing agent. The reaction is typically carried out at room temperature.

The starting aldehydes of the formula (II) wherein X is CH<sub>2</sub> can be prepared by the method shown in the Scheme I and the aldehydes of the formula (II) wherein X is C=O by the method shown in Scheme 2:

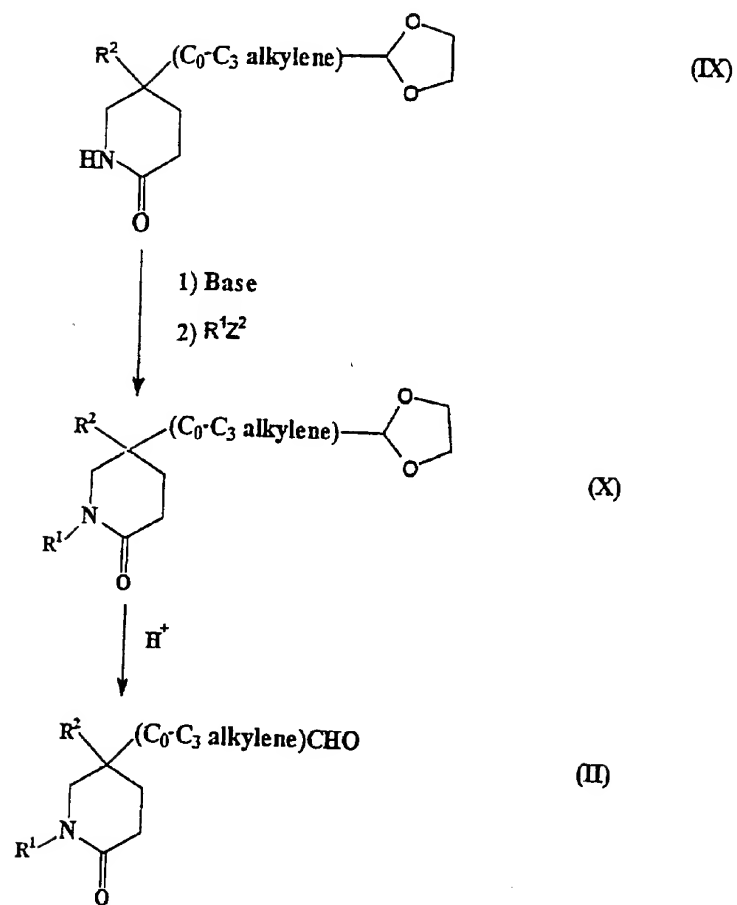
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SCHEME I



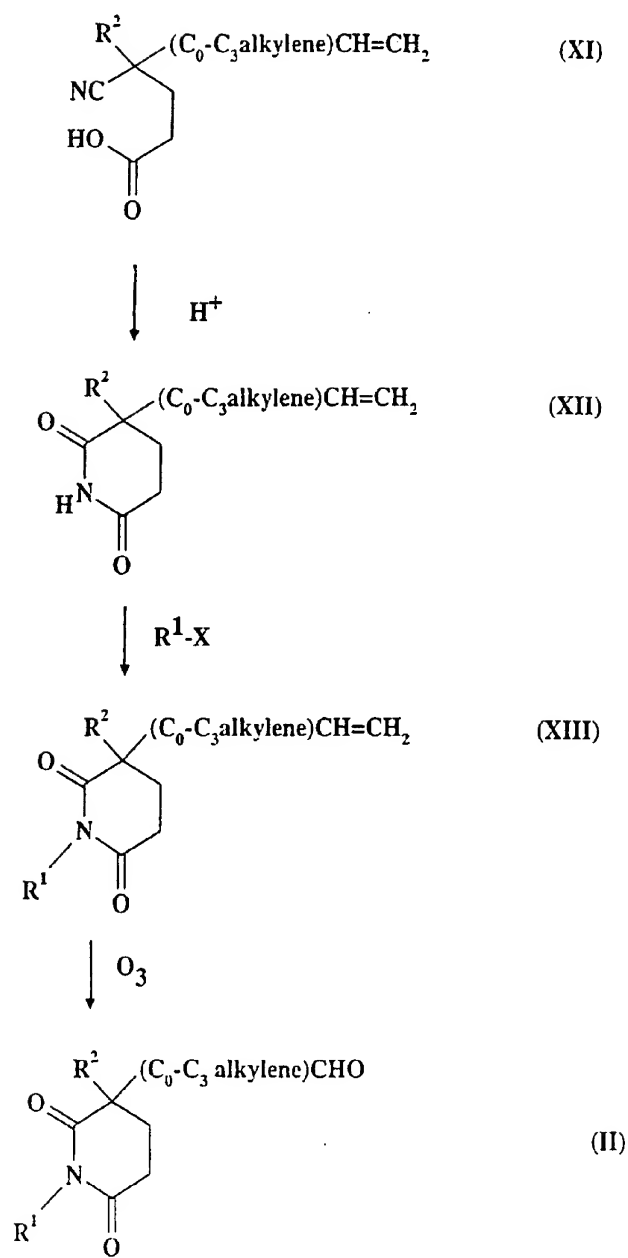
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## SCHEME I (continued)



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## SCHEME 2



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where  $R^1$  and  $R^2$  are as previously defined for a compound of the formula (I) and Z,  $Z^1$  and  $Z^2$  are each a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethylsulphonyloxy.

- 5 In a typical procedure, an arylmethylnitrile of formula (IV) is first deprotonated using a suitable base, e.g. sodium hydride or lithium hexamethyldisilylazide, and then alkylated in situ with an alkylating agent of the formula (V) where Z is preferably bromo. The reaction is typically carried out in a suitable solvent, e.g. tetrahydrofuran, at about 5°C for the deprotonation and at about
- 10 room temperature for the alkylation. The acetonitrile derivative of the formula (VI) that is produced is then first deprotonated using a suitable base, e.g. lithium diisopropylamide or lithium hexamethyldisilylazide, and then alkylated in situ with a compound of the formula (VII) where  $Z^1$  is preferably bromo. The reaction is typically carried out in a suitable solvent, e.g. tetrahydrofuran, at about 5°C,
- 15 warming to about room temperature to complete the reaction. Tetra-n-butylammonium iodide can optionally be added following addition of the compound of the formula (VII) to increase the rate of reaction. Finally an aqueous base is added e.g. sodium hydroxide, to produce the carboxylic acid of formula (VIII). The product can be resolved at this stage, if desired, for example by
- 20 fractional crystallisation of an optically active salt.

The compound of the formula (VIII) prepared is then reduced and cyclised to a pyridone of the formula (IX) under suitable conditions, e.g. using platinum oxide under an atmosphere of hydrogen at atmospheric pressure and room temperature using glacial acetic acid as the solvent.

- 25 The pyridone of the formula (IX) is then first deprotonated using a suitable base, e.g. potassium hydride, and then N-alkylated in situ with a compound of the formula  $R^1Z^2$  where  $Z^2$  is preferably bromo, methanesulphonyloxy or p-toluenesulphonyloxy. The reaction is typically carried out in a suitable solvent, e.g. dimethylsulphoxide, and at about room temperature.

- 30 The product of the formula (X) produced is then treated with aqueous hydrochloric acid in a suitable solvent e.g. tetrahydrofuran, to remove the dioxolane protecting group and yield the aldehyde product of formula (II).

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Compounds of the formula (II) wherein X is C = O may be prepared in a similar manner by cyclisation of a 4-cyano-4-aryl-hept-6-enoic (XI), prepared as described in WO 96/05193, followed by N-alkylation and ozonolysis of the

5 resulting 3-allyl-glutaramide (XIII).

Preparation of the azabicyclo[3.1.0]hexane starting material of formula (III) wherein R<sup>3</sup> is t-butoxycarbonylamino is described in WO93/18001. This may be used as starting material to prepare further intermediates of formula (III) wherein R<sup>3</sup> is as defined above. Thus for example the compound is first N-protected by

10 reaction with benzylchloroformate and the t-butoxycarbonyl group removed by treatment with gaseous hydrogen chloride. The resulting 1-benzyloxycarbonyl-1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,6-amino-3-azabicyclo[3.1.0]hexane may then be reacted to introduce various R<sup>3</sup> substituent groups. Thus for example reaction with bis-chloroethyl ether and tetra-n-butylbromide by refluxing in dioxan in the presence of sodium

15 hydroxide solution yields 1-benzyloxycarbonyl-1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,6-morpholino-3-azabicyclo[3.1.0]hexane. Removal of the benzyloxycarbonyl group by catalytic hydrogenation yields the compound of formula (III) when R<sup>3</sup> is a morpholino group.

20 As an alternative to the above process, in the case of the compounds of formula (I) wherein R<sup>3</sup> is NH<sub>2</sub>, they may be obtained, for example from the corresponding compound of formula (I) wherein R<sup>3</sup> is t-butoxycarbonylamino by deprotection, using for example trifluoroacetic acid. This process may be adapted to use other amino-protected groups present as the R<sup>3</sup> substituent and

25 appropriate protecting groups and methods for their removal will be well known to those skilled in the art. This product may be used in turn to prepare further compounds of formula (I). Thus for example in the case of compounds of the formula (I) wherein R<sup>3</sup> is -NR<sup>4</sup>SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -NR<sup>4</sup>SO<sub>2</sub>aryl, -NR<sup>4</sup>CO(C<sub>1</sub>-C<sub>6</sub> alkyl) or NR<sup>4</sup>COaryl, the compounds may be prepared from the corresponding

30 compound where R<sup>3</sup> is NH<sub>2</sub> by sulphonylation or acylation with the appropriate sulphonylchloride or acylchloride. Thus for example reaction of the compound of formula (I) wherein R<sup>3</sup> is NH<sub>2</sub> with a C<sub>1</sub>-C<sub>6</sub> alkyl or aryl-sulphonylchloride gives the corresponding compound of formula (I) wherein R<sup>3</sup> is NH-SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl) or

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NHSO<sub>2</sub> aryl. The reaction is typically conducted in an organic solvent such as dichloromethane in the presence of an acid acceptor such as triethylamine and is generally complete after several hours at room temperature. Similarly reaction of the amine of formula (I) wherein R<sup>3</sup> is NH<sub>2</sub> with a C<sub>1</sub>-C<sub>6</sub> acyl or aroylchloride gives the corresponding compounds of formula (I) wherein R<sup>3</sup> is NHCO(C<sub>1</sub>-C<sub>6</sub> alkyl) or NHCO aryl. Alkylation of the above products, for example using a C-C<sub>6</sub> alkyl bromide yields the corresponding compounds wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl.

10 All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and to the Examples and Preparations hereto.

15

A pharmaceutically acceptable acid addition or base salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

20

The high activity of the compounds of the invention as neurokinin receptor antagonists is demonstrated by the following procedures:

The affinity of the compounds of formula (I) and their salts for the human NK<sub>1</sub> receptor can be tested in vitro by measuring their ability to inhibit [<sup>3</sup>H]-Substance P binding to membranes prepared from the human IM9 cell line expressing the human NK<sub>1</sub> receptor using a modification of the method described in McLean, S. et al, J. Pharm. Exp. Ther., 267, 472-9 (1993) in which, instead of using whole cells, the cells are homogenised using a tissue homogeniser, and the particulate fraction is pelleted by centrifugation and washed three times with buffer prior to resuspension of the membranes.

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- The affinity of the compounds of formula (I) and their salts for the human NK<sub>2</sub> receptor can be measuring in vitro by testing their ability to compete with [<sup>3</sup>H] or [<sup>125</sup>I]NKA (neurokinin A) for binding to membranes prepared from Chinese hamster ovary cells expressing the cloned human NK<sub>2</sub> receptor. In this method, washed Chinese hamster ovary cell membranes are prepared as described for the previous method where IM9 cells are used instead. The membranes are incubated (90 min, 25°C) with [<sup>125</sup>I] NKA and a range of concentrations of the test compound. Non-specific binding was determined in the presence of 10µM NKA.
- 10 The NK<sub>2</sub> receptor antagonist activity of the compounds of the formula (I) can also be measured, in vitro, by testing their ability to antagonise the contractile effects of the selective NK<sub>2</sub> receptor agonist [ $\beta$ Ala<sup>8</sup>]NKA<sub>(4-10)</sub> (Rovereo, P. et al, Neuropeptides, 13, 263-270, 1989) in the rabbit pulmonary artery, using the method of Patacchini and Maggi, Eur. J. Pharmacol., 236, 31-37 (1993).
- 15 The compounds of the formula (I) and their salts can be tested for NK<sub>2</sub> receptor antagonist activity, in vivo, by measuring their ability to inhibit bronchoconstriction induced by [ $\beta$ Ala<sup>8</sup>]NKA<sub>(4-10)</sub> in the anaesthetised guinea pig, using the method described by Murai et al, J. Pharm. Exp. Ther., 262, 403-408 (1992) or Metcalfe et al, Br. J. Pharmacol., 112, 563P (1994).
- 20 The compounds of the formula (I) and their salts can be tested for NK<sub>3</sub> receptor antagonist activity, in vitro, by measuring their ability to antagonise the contractile effects of the selective NK<sub>3</sub> receptor agonist senktide in the guinea-pig ileum using the method of Maggi et al, Br. J. Pharmacol., 101, 996-1000 (1990).
- 25 For human use, the compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutically acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing
- 30 such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. They can be injected parenterally, for

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example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) and their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.5 to 5, and most preferably from 1 to 2, mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time, as appropriate. In any event, the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient and disease being treated. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the compounds of the formula (I) can be administered by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required. Such formulations will be selected as appropriate to the particular disease being treated and mode of administration required.

It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of the disease.

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Thus the invention further provides:-

- 5 i) a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier;
- ii) a compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, for use as a medicament;
- 10 iii) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin acting at the human NK<sub>1</sub>, NK<sub>2</sub> or NK<sub>3</sub> receptor, or a combination thereof;
- 15 iv) use as in (iii) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, 20 an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.
- 25 v) a method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin acting at the human NK<sub>1</sub>, NK<sub>2</sub> or NK<sub>3</sub> receptor, or a combination thereof, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;
- 30 vi) a method as in (v) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous



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5 system disorder such as anxiety, depression, dementia or psychosis,  
a gastro-intestinal disorder such as functional bowel disease, irritable bowel  
syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's  
disease, an urogenital tract disorder such as incontinence, hyperreflexia or  
cystitis, a pulmonary disorder such as chronic obstructive airways disease,  
an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity  
disorder such as to poison ivy, a peripheral neuropathy such as diabetic  
neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic  
10 neuralgia or post-herpetic neuralgia, cough or acute or chronic pain;

The following Examples illustrate the preparation of the compounds of the formula  
(I):-

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EXAMPLE 15(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-morpholino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone

- 5 A solution of 5(S)-1-cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-formylmethyl-2-piperidone (130 mg, 0.38 mmol) (see preparation 5) and 1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-morpholino-3-azabicyclo[3.1.0]hexane (see preparation 4) in tetrahydrofuran was stirred for 30 minutes at room temperature. Sodium triacetoxyborohydride (120 mg, 1.5 mol equivalents) and glacial acetic acid (0.021 ml) were added and the
- 10 mixture stirred for one hour. Water (1 ml) was added followed by saturated sodium carbonate solution (10 ml) and the mixture extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried over magnesium sulphate, filtered, and the solvent removed from the filtrate under reduced pressure. The residue was chromatographed on silica gel eluting with a solvent gradient of
- 15 methanol to methylene chloride (5:95, 10:90), to give the title compound (100 mg). TLC R<sub>F</sub> = 0.3 (silica, methanol:dichloromethane 10:90 by volume). LRMS m/z = 492 (m+1)<sup>+</sup>. Found: C,60.68; H,6.91; N,7.97. C<sub>26</sub>H<sub>35</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>. 0.33 CH<sub>2</sub>Cl<sub>2</sub> requires C,60.70; H,6.91; N,8.07%. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 0.2-0.4(m,2H), 0.5-0.7(m,2H), 1.0-1.05(m,1H), 1.4(s,2H), 1.6(s,2H), 1.7-1.9(m,2H), 2.0-2.2(m,6H),
- 20 2.3-2.49(m,1H), 2.5(m,4H), 2.8-2.9(dd,2H), 3.2(m,1H), 3.4-3.5(m,2H), 3.65(m,4H), 3.8(d,1H), 7.1(dd,1H), 7.4(m,2H)ppm.

EXAMPLE 25(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-t-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone

- 25 A solution of 5(S)-1-cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-formylmethyl-2-piperidone (1.5 g, 4.41 mmol) (see preparation 5) and 1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-t-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane (see preparation 4) in tetrahydrofuran was stirred for 40 minutes at room temperature. Sodium triacetoxyborohydride (1.4 g, 1.5 mol equivalents) and glacial acetic acid (0.24 ml)
- 30 were added and the mixture stirred for eighteen hours. Saturated sodium carbonate solution (20 ml) was added and the mixture extracted with ethyl acetate

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(3 x 40 ml). The combined organic extracts were dried over magnesium sulphate, filtered, and the solvent removed from the filtrate under reduced pressure. The residue was chromatographed on silica gel eluting with a solvent gradient of

5 methanol to ethyl acetate (5:95, 10:90), to give the title compound (1.1 g). TLC  $R_f$  = 0.1-0.2 (silica, ethyl acetate:methanol, 90:10 by volume). LRMS  $m/z$  = 522 ( $m = 1$ )<sup>+</sup>. Found: C, 61.74; H, 7.47; N, 7.99.  $C_{27}H_{37}Cl_2N_3O_3$  requires C, 62.05; H, 7.14; N, 8.04%. <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  = 0.2-0.4(m, 2H), 0.5-0.7(m, 2H), 1.0-1.05(m, 1H), 1.3(m, 1H), 1.4(s, 9H), 1.7(m, 1H), 1.9(m, 1H), 2.0-2.2(m, 8H), 2.3-

10 2.35(m, 1H), 2.65(s, 1H), 2.9-3.0(dd, 2H), 3.1-3.2(m, 1H), 3.4-3.5(m, 2H), 3.8(d, 1H), 4.4-4.6(s, br, 1H), 7.1(dd, 1H), 7.4(m, 2H) ppm.

EXAMPLE 3

5(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-amino-3-

15 azabicyclo[3.1.0]hexane]ethyl)-2-piperidone di-trifluoroacetate salt

To a solution of the compound from example 2, (1.0 g, 1.92 mmol), in methylene chloride was added trifluoroacetic acid (2.2 ml, 15 mol equivalents) with ice bath cooling. The reaction was allowed to warm to room temperature overnight. The reaction mixture was evaporated under reduced pressure and

20 then re-evaporated from methylene chloride and then diethyl ether, to give a gum, 1.2 g. TLC  $R_f$  = 0.2 (silica, methylene chloride:methanol, 90:10 by volume). LRMS  $m/z$  = 422 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H-NMR(CDCl<sub>3</sub>)  $\delta$  = 0.2-0.4(m, 2H), 0.5-0.6(m, 2H), 0.95-1.05(m, 1H), 1.8-2.3(m, 10H), 2.6-2.8(m, 3H), 3.0-3.3(m, 3H), 3.4-3.8(m, 3H), 7.47(d, 1H), 7.6(m, 2H), 8.3(s, br, 3H), 10(s, broad, 0.5H), 10.5(s, broad, 0.5H) ppm.

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EXAMPLE 4

5(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-amino-3-

azabicyclo[3.1.0]hexane]ethyl)-2-piperidone

The compound from example 3 (400 mg) was dissolved in methylene

30 chloride and washed with sodium hydrogen carbonate solution. The organic layer

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was separated, dried over magnesium sulphate, filtered under reduced pressure and evaporated under reduced pressure to give a gum. This was chromatographed on silica eluting with a solvent gradient of methylene chloride to methanol (95:5, 90:10) to give the title compound (200 mg). TLC  $R_F$  = 0.1 (silica, methylene chloride:methanol, 90:10 by volume). LRMS  $m/z$  = 422 ( $M+1$ )<sup>+</sup>. Found: C, 59.27; H, 6.47; N, 9.58.  $C_{22}H_{29}Cl_2N_3O$ . 0.25  $CH_2Cl_2$  requires C, 59.54; H, 6.70; N, 9.47%. <sup>1</sup>H-NMR ( $CDCl_3$ )  $\delta$  = 0.2-0.4(m, 2H), 0.5-0.7(m, 2H), 1.0-1.1(m, 1H), 1.3(s, 2H), 1.4-1.7(br, s, 3H), 1.7-1.8(m, 1H), 1.8-1.9(m, 1H), 1.9-2.2(m, 6H), 2.5-2.7(m, 2H), 2.8-3.0(m, 2H), 3.1-3.2(m, 1H), 3.4-3.5(m, 2H), 3.7-3.9(m, 1H), 7.1-7.2(m, 1H), 7.4(m, 2H) ppm.

#### EXAMPLE 5

5(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-methanesulphonylamino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone

To a solution of the compound from example 3 (450 mg, 0.69 mmol) and triethylamine (0.45 ml, 4.5 mole equivalents) in methylene chloride (15 ml) was added methanesulphonyl chloride (0.1 ml, 2 mol equivalents). The mixture was stirred for thirty minutes and stood at room temperature overnight. The reaction mixture was diluted with methylene chloride and washed with water (15 ml). The organic layer was dried over magnesium sulphate, filtered under reduced pressure and the solvent removed under reduced pressure to give a gum. This was chromatographed on silica eluting with solvent gradient of ethyl acetate to methanol, (90:10, 80:20) to give the title compound as a foam (95 mg) after re-evaporation from diethyl ether. TLC  $R_F$  = 0.5 (silica, methylene chloride:methanol, 90:10 by volume). LRMS  $m/z$  = 500 ( $M+1$ )<sup>+</sup>. Found: C, 54.23; H, 6.04; N, 8.13.  $C_{23}H_{31}Cl_2N_3O_3S$ . 0.5  $H_2O$  requires C, 54.21; H, 6.33; N, 8.25%. <sup>1</sup>H-NMR ( $CDCl_3$ )  $\delta$  = 0.4-0.6(m, 2H), 0.5-0.7(m, 2H), 1.0-1.1(m, 1H), 1.7(s, 3H), 1.8-2.4(m, 9H), 2.7(br, s, 2H), 3.0(s, 4H), 3.1-3.2(m, 1H), 3.4-3.5(m, 2H), 3.75(d, 1H), 4.5(s, 1H), 7.1(m, 1H), 7.35-7.45(m, 2H) ppm.

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EXAMPLE 6

5(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-pentafluorophenylsulphonylamino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone

- 5 To a solution of the compound from example 3 (1.0 g, 1.53 mmol) and triethylamine (0.68 ml, 3.2 mole equivalents) in methylene chloride (15 ml) was added pentafluorophenylsulphonyl chloride (0.49 g, 1.2 mol equivalents). The mixture was stirred for thirty minutes and stood at room temperature overnight. The reaction mixture was diluted with methylene chloride and washed with water
- 10 (15 ml). The organic layer was dried over magnesium sulphate, filtered under reduced pressure and the solvent removed under pressure to give a gum. This was chromatographed on silica eluting with solvent gradient of ethyl acetate to methanol, (90:10, 80:20). The compound was triturated with ethyl acetate and diethyl ether and the white solid obtained filtered and discarded. The filtrate was
- 15 evaporated and rechromatographed on silica eluting with a solvent gradient of methylene chloride to methanol 90:10. LRMS  $m/z = 652(M+1)^+$ . Found: C, 51.83; H, 4.24; N, 6.32.  $C_{28}H_{28}Cl_2F_5N_3O_3S$  requires C, 51.53; H, 4.32; N, 6.44%.  $^1H$ -NMR ( $CDCl_3$ )  $\delta = 0.4$ - $0.6$ (m, 2H),  $0.5$ - $0.7$ (m, 2H),  $1.0$ - $1.1$ (m, 1H),  $1.5$ (s, 2H),  $1.6$ - $1.9$ (m, 2H),  $1.9$ - $2.2$ (m, 8H),  $2.3$ - $2.4$ (m, 1H),  $2.5$ (s, 1H),  $2.9$ (m, 2H),  $3.35$ - $3.5$ (m, 2H),
- 20  $3.75$ (d, 1H),  $5.3$ (d, 1H),  $7.1$ (m, 1H),  $7.35$ - $7.45$ (m, 2H) ppm.

EXAMPLE 7

5(S)-5-(3,4-Dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -4'-fluorophenylsulphonylamino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone

- 25 To a solution of the compound from example 3 (1.0 g, 1.53 mmol) and triethylamine (0.86 ml, 4 mole equivalents) in methylene chloride (15 ml) was added 4-fluorophenylsulphonyl chloride (0.36 g, 1.2 mol equivalents). The mixture was stirred at room temperature for five hours and stood at room temperature overnight. The reaction mixture was diluted with methylene chloride
- 30 and washed with water (2 x 20 ml). The organic layer was dried over magnesium sulphate, filtered under reduced pressure and the solvent removed under reduced

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pressure to give a gum. This was chromatographed on silica eluting with solvent gradient of methylene chloride to methanol, (95:5, 92:8) to give the title compound as a gum (140 mg). TLC  $R_F$  = 0.5 (silica, methylene chloride:methanol, 90:10 by volume). LRMS  $m/z$  = 580 ( $M+1$ )<sup>+</sup>. Found: C, 57.17; H, 5.56; N, 7.09.

$C_{28}H_{32}FCl_2N_3O_3 \cdot 0.25 H_2O$  requires C, 57.47; H, 5.60; N, 7.18%. <sup>1</sup>H-NMR ( $CDCl_3$ )  $\delta$  = 0.4-0.6(m, 2H), 0.5-0.7(m, 2H), 1.0-1.1(m, 1H), 1.7(s, 3H), 1.6-2.0(m, 1H), 2.0-2.25(m, 7H), 2.3-2.4(m, 2H), 2.8-2.9(m, 2H), 3.0-3.2(m, 1H), 3.4-3.6(m, 2H), 3.7(d, 1H), 4.6(s, 1H), 7.1(m, 1H), 7.2-7.3(m, 2H), 7.35-7.45(m, 2H), 7.85-7.95(m, 2H) ppm.

### EXAMPLE 8

5(S)-5-(3,4-Dichlorophenyl)-1-cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6,4'-fluorophenylcarboxyamido-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone  
trifluoroacetate salt

To a solution of the compound from example 3 (300 mg, 0.46 mmol) and triethylamine (0.26 ml, 4 mole equivalents) in methylene chloride (15 ml) was added 4-fluorobenzoyl chloride (0.07 ml, 1.2 mol equivalents). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride and washed with water (2 x 20 ml). The organic layer was dried over magnesium sulphate, filtered under reduced pressure and the solvent removed under reduced pressure to give a gum. This was chromatographed on silica eluting with solvent gradient of ethyl acetate to methanol, (90:10, 80:20) to give the title compound as a gum (100 mg). TLC  $R_F$  = 0.1-0.2 (silica, ethyl acetate:methanol, 90:10 by volume). LRMS  $m/z$  = 544 ( $M+1$ )<sup>+</sup>. Found: C, 56.06; H, 4.83; N, 5.99.  $C_{29}H_{32}FCl_2N_3O_2$  monotrifluoroacetate salt. 0.02 ethyl acetate requires C, 55.76; H, 4.71; N, 6.22%. <sup>1</sup>H-NMR ( $CDCl_3$ )  $\delta$  = 0.2-0.3(m, 2H), 0.4-0.5(m, 2H), 0.9-1.1(m, 1H), 1.5(s, 2H), 1.6-1.9(m, 3H), 1.9-2.1(m, 1H), 2.1-2.3(m, 6H), 2.85-3.0(m, 3H), 3.1-3.2(m, 1H), 3.5(d, 2H), 3.8(d, 1H), 7.1-7.3(m, 2H), 7-7.4(m, 1H), 7.5-7.7(m, 2H), 7.85-7.9(m, 2H), 8.3(d, 1H) ppm.

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EXAMPLE 9

5-(3,4-Dichlorophenyl)-1-benzyl-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-morpholino-3-azabicyclo[3.1.0]hexane] ethyl)-2-piperidone

- 5 A solution of 1-benzyl-5-(3,4-dichlorophenyl)-5-formylmethyl-2-piperidone (0.28 g, 0.75 mmol) (see preparation 6) and 1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-morpholino-3-azabicyclo[3.1.0]hexane (0.14 g, 0.83 mmol) (see preparation 4) in tetrahydrofuran was stirred for 45 minutes. Sodium triacetoxyborohydride (245 mg, 1.5 mol equivalents) and glacial acetic acid (0.045 ml) were  
10 added and the mixture stirred for one hour. Saturated sodium carbonate solution (10 ml) was added and the mixture extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried over magnesium sulphate, filtered, and the solvent removed from the filtrate under reduced pressure. The residue was chromatographed on silica gel eluting with a solvent gradient of methanol to  
15 methylene chloride (2:98, 5:95, 10:90), to give the title compound (235 mg). TLC  $R_F$  = 0.3 (silica, methanol:dichloromethane 10:90 by volume). Found: C,66.14; H,6.88; N,7.81.  $C_{29}H_{35}Cl_2N_3O_2$  requires C,65.89; H,6.67; N,7.95%.  $^1H$ -NMR ( $CDCl_3$ )  $\delta$  = 1.4 (s,2H), 1.5-1.8(m,2H), 1.9-2.1(m,4H), 2.1-2.25(m,4H), 2.3-2.4(m,1H), 2.5-2.6(m,4H), 2.7-2.9(m,2H), 3.3(d,1H), 3.5-3.6(d,1H), 3.6-3.7(m,4H),  
20 4.35(d,1H), 4.85(d,1H), 6.8(m,1H), 7.1(m,1H), 7.2-7.5(m,6H) ppm.

EXAMPLE 10

3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-morpholino-3-azabicyclo[3.1.0]hexane]ethyl)glutarimide

- 25 The procedure of Example 1 was followed starting with 3(S)-1-cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-formylmethyl-glutarimide (see preparation 7) to yield the title compound as a gum. Found: C,60.71; H,6.24; N,7.20.  $C_{26}H_{33}Cl_2N_3O_3 \cdot 0.5 H_2O$  requires C,60.58; H,6.64; N,8.15%.  $^1H$ -NMR ( $CDCl_3$ ): 0.25-0.55(m,4H), 1.1-1.3(m,H), 1.5-1.6(m,8H), 1.8-2.0(m,2H), 2.1-2.7(m,11H), 2.9-3.0(m,2H), 3.6-3.65(m,4H), 3.7-3.8(m,2H), 7.0-7.05(m,1H), 7.35-7.4(m,2H).
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PREPARATION 11-Benzylloxycarbonyl-1 $\alpha$ .5 $\alpha$ .6 $\alpha$ -6-t-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane

- 5        Benzylchloroformate (1.10 ml, 7.8 mmol) was added to an ice-cooled solution of 1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ -6-t-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane (1.4 g, 7.1 mmol) (prepared as described in WO93/18001) and triethylamine (1.1 ml, 7.8 mmol) in dichloromethane (35 ml). The reaction was stirred for one hour and then water was added, the organic layer was washed with water, dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give the title compound as a gum (3.0 g). TLC  $R_F$  = 0.6 (silica, methanol: dichloromethane 5:95 by volume). LRMS  $m/z$  = 350(MNH<sub>4</sub>)<sup>+</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 1.4(s,9H), 1.7(s,2H), 2.3(s,1H), 3.5(m,2H), 3.7(m,2H), 4.6(m,1H), 5.1(s,2H), 7.3(m,5H)ppm.
- 10

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PREPARATION 21-Benzylloxycarbonyl-1 $\alpha$ .5 $\alpha$ .6 $\alpha$ -6-amino-3-azabicyclo[3.1.0]hexane

- Hydrogen chloride gas was bubbled through a solution of the compound from preparation 1 (3.0 g) in ethyl acetate (40 ml) with ice-cooling. After one hour the ethyl acetate was evaporated and the residue partitioned between methylene chloride and 10% sodium carbonate solution. The organic layer was dried over magnesium sulphate, filtered, and the solvent removed under reduced pressure to give an oil, (1.4 g). TLC  $R_F$  = 0.3 (silica, methanol:dichloromethane 5:95 by volume). <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  = 1.7(s,1H), 1.9(s,3H), 2.1(s,1H), 3.4-3.8(m,4H), 5.1(m,2H), 7.3(m,5H) ppm.
- 20

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PREPARATION 31-Benzylloxycarbonyl-1 $\alpha$ .5 $\alpha$ .6 $\alpha$ -6-morpholino-3-azabicyclo[3.1.0]hexane

- The compound from preparation 2 (1.4 g, 6.03 mmol), bis-chloroethylether (1.1 ml, 9.1 mmol), and tetra-n-butylbromide (200 mg) were refluxed together in a solution of dioxan (30 ml) and 2N sodium hydroxide solution for 18 hours. After this time further bis-chloroethyl ether (1.1 ml) was added reflux continued for a
- 30



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- further 18 hours followed by the addition of a further portion of bis-chloroethylether (1.1 ml) and further reflux for 18 hours. The dioxan was evaporated under reduced pressure and the residue partitioned between
- 5 methylene chloride and water. The organic layer was separated, dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was chromatographed on silica using a gradient elution of methylene chloride to methanol (98:2, 95:5), to give the product fractions as an oil which crystallised on standing. (0.68 g). TLC  $R_F$  = 0.5 (silica,
- 10 methanol:dichloromethane 5:95 by volume). LRMS  $m/z$  = 303 ( $m+1$ )<sup>+</sup>. <sup>1</sup>H-NMR(CDC1<sub>3</sub>)  $\delta$ =1.5(s,1H), 1.8(m,2H), 2.5-2.6(m,3H), 3.4-3.5(m,2H), 3.5-3.7(m,7H), 5.1(s,2H), 7.3(m,5H) ppm.

#### PREPARATION 4

- 15 1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,6-morpholino-3-azabicyclo[3.1.0]hexane

A solution of the compound from preparation 3 (0.65 g, 2.1 mmol) in ethanol (50 ml) was added to 5% palladium on carbon (300 mg) and the mixture stirred under an atmosphere of hydrogen at 345 kPa (50 psi) and at room temperature for 18 hours. The catalyst was removed by filtration and the solvent removed

20 under reduced pressure to give an oil (0.35 g) which crystallised on standing overnight. <sup>1</sup>H-NMR(CDC1<sub>3</sub>)  $\delta$  = 1.5-1.6(m,3H), 2.2-2.4(br,s,1H), 2.5-2.6(m,4H), 2.9-3.1(m,4H), 3.6-3.8(m,4H).

#### PREPARATION 5

- 25 5(S)-1-Cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-formylmethyl-2-piperidone  
 (a) 4(S)-4-Cyano-4-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-yl)pentan-1-oic acid

To a 1.0 M solution of lithium hexamethyldisilylazide in tetrahydrofuran (4.69 l) at 5°C under nitrogen was added a solution of 3,4-dichlorophenylacetonitrile (750 g, 4.28 moles) in tetrahydrofuran (750 ml),

30 dropwise, over 45 minutes. The reaction was allowed to stir for 2 hours.

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The reaction was cooled again to 5°C and a solution of 2-bromomethyl-1,3-dioxolane (782 g) in tetrahydrofuran (780 ml) added, dropwise, over fifty minutes. Tetra-n-butylammonium iodide (75 g) was added, portionwise, and the mixture allowed to warm to room temperature and stirred for 14 hours. The reaction was then cooled to 5°C and a 1.0M solution of lithium hexamethyldisilylazide in tetrahydrofuran (4.69 l) was added, dropwise. The mixture was stirred for 5 hours at room temperature. The solution was cooled to 5°C and a solution of ethyl 3-bromopropanoate (840.5 g) in tetrahydrofuran (840 ml) was added, dropwise, over 50 minutes. The reaction was allowed to stir for 14 hours. The reaction mixture was cooled to 5°C and 1.5M aqueous sodium hydroxide solution (containing 255 g of sodium hydroxide) was added and the mixture stirred for 14 hours. Water (5 l) was added and the mixture was extracted with ethyl acetate (2 x 3 l). The combined organic extracts were washed with water (2 x 5 l). The aqueous phases were combined and acidified to pH1 using 5N aqueous hydrochloric acid solution and then extracted with ethyl acetate (2 x 3 l). The combined organic extracts were concentrated under reduced pressure to a concentration of approximately 3 ml/g based on the theoretical yield of the product.

The above experimental procedure was then repeated on an identical scale. To the combined organic solutions from both reactions was added (S)-(-)-alpha-methylbenzylamine (1.13 kg) and the mixture stirred for 14 hours. The thick slurry was then stirred with cooling in an ice-bath for 2 hours, filtered, the solid washed with ethyl acetate (2 x 1 l) and then dried under reduced pressure at 35°C to give 1.85 kg of material.

A portion of this material (1.34 kg) was dissolved in a mixture of butanone (2 l) and water (503 ml) that was heated under reflux. A further portion of butanone (4.7 l) was added and the solution was allowed to cool slowly to room temperature overnight. The resulting solid was filtered, washed with butanone (2 x 1 l) and dried under reduced pressure at 35°C for 10 hours to give 563 g of material (93.8%). A further recrystallisation from

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butanone/water gave the title compound as a (S)-(-)-alpha-methylbenzylamine salt in 99.8% yield. To a stirred solution of this salt in ethyl acetate and water was added 5N aqueous hydrochloric solution until pH1 was achieved. The mixture was stirred for a further 30 minutes, the layers separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were washed with water and the solvent removed by evaporation under reduced pressure to give the title compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 2.05-2.35(m,4H), 2.4-2.65(m,2H), 3.7-4.0(m,4H), 4.75-4.85(m,1H), 7.25-7.55(m,3H), 9.9(s,br.,1H,acid) ppm.

(b) 5(S)-5-(3,4-Dichlorophenyl)-5-(1,3-dioxolan-2-ylmethyl)-2(1H)-piperidone

To a solution of the above compound (13.5 g, 39.22 mmol) in glacial acetic acid (130 ml) was added platinum oxide (1.21 g) and the mixture stirred under an atmosphere of hydrogen at 414 kPa (60 psi) and at room temperature for 17 hours. The catalyst was removed by filtration and a further portion of platinum oxide (1.21 g) added. The reaction mixture was then stirred under an atmosphere of hydrogen 414kPa (60 psi) and at room temperature for 48 hours. The catalyst was removed by filtration and the solution concentrated under reduced pressure. The residue was dissolved in ethyl acetate (80 ml) and washed with saturated aqueous sodium bicarbonate solution (2 x 75 ml). The organic phase was then separated and the solvent removed under reduced pressure. The resulting solid was stirred in a solution of hexane (20 ml) and ethyl acetate (20 ml) for 2 hours at 0°C and then filtered off to give the title compound (8.15 g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 1.85-1.95(m,1H), 2.0-2.25(m,4H), 2.35-2.4(m,1H), 3.45-3.55(m,1H), 3.65-3.75(m,2H), 3.8-3.9(m,3H), 4.35-4.4(m,1H), 6.15(s,br.,1H), 7.2-7.45(m,3H) ppm.

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(c) 5(S)-1-Cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-(1,3-dioxolan-2-ylmethyl)-2-piperidone

5 To a solution of the above compound (38.6 g, 117 mmol) in dimethyl sulphoxide (190 ml) was added potassium hydroxide (19.7 g) and the mixture stirred at room temperature for 20 minutes.

10 Bromomethylcyclopropane (17.37 g) was then added over 20 minutes and the reaction stirred for a further 140 minutes. The reaction was poured into a mixture of ice (100 g) and water (900 ml) and the mixture extracted with dichloromethane (2 x 400ml). The combined organic layers were washed with water (400 ml) and the solvent removed under reduced pressure to give the title compound (45.4 g).

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 0.3-0.4(m,2H), 0.55-0.65(m,2H), 1.05-1.15(m,1H), 1.9-1.95(m,1H), 2.0-2.25(m,4H), 2.35-2.45(m,1H), 3.15-3.2(m,1H), 3.5-3.55(m,2H), 3.65-3.75(m,2H), 3.9-4.0(m,3H), 4.35-4.4(m,1H), 7.2-7.5(m,3H) ppm.

(d) 5(S)-1-Cyclopropylmethyl-5-(3,4-dichlorophenyl)-5-formylmethyl-2-piperidone

20 To a solution of the above compound of (73.16 g, 190 mmol) in tetrahydrofuran (730 ml) at 5°C was added 5N aqueous hydrochloric acid solution (730 ml) over 20 minutes. The reaction mixture was stirred at room temperature for 17 hours. The tetrahydrofuran was removed under reduced pressure, the residue diluted with water (200 ml) and extracted with ethyl acetate (2 x 500 ml). The combined organic layers were then washed with water (500 ml) and the solvent removed under reduced pressure to give the title compound (62.1 g).

25 <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 0.25-0.35(m,2H), 0.55-0.65(m,2H), 1.05-1.1(m,1H), 2.15-2.25(m,3H), 2.35-2.5(m,1H), 2.65-2.75(m,1H), 2.95-3.05(m,1H), 3.15-3.2(m,1H), 3.45-3.6(m,2H), 3.95-4.0(m,1H), 7.2-7.45(m,3H), 9.5(s,1H) ppm.

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PREPARATION 61-Benzyl-5-(3,4-dichlorophenyl)-5-formylmethyl-2-piperidone

The procedure of preparation 5 was followed using benzylbromide in step (c) instead of bromomethylcyclopropane and omitting the salt resolution in step (a), to give the title compound as a gum. LRMS  $m/z=376(m+1)^+$ .  $^1H$ -NMR  $\delta=2.1-2.3(m,3H)$ ,  $2.4-2.55(m,2H)$ ,  $2.6(dd,1H)$ ,  $2.85(dd,1H)$ ,  $3.4(d,1H)$ ,  $3.75(d,1H)$ ,  $4.45(d,1H)$ ,  $4.8(d,1H)$ ,  $6.85(m,1H)$ ,  $7.25-7.4(m,7H)$  ppm.

PREPARATION 73(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-formylmethyl-glutarimide(a) 3(S)-3-Allyl-3-(3,4-dichlorophenyl)-(1H)glutarimide

A solution of 4(S)-4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid (3.4 g, 11.4 mmol), formic acid (4 ml), and hydrochloric acid (2 ml) in dimethylformamide (23 ml) was heated at 145°C for 48 hours. The solution was cooled to room temperature and water (50 ml) added. The mixture was basified using 15% aqueous sodium carbonate solution until an oily precipitate formed and then extracted with ethyl acetate (2 x 50 ml). The combined organic phases were dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to give an oil which was purified by flash column chromatography on silica gel using hexane:ethyl acetate (3:1, by volume) as eluant to give the title compound (1.62 g). TLC Rf = 0.87 (silica, ethyl acetate:hexane 1:3, by volume). m.p. = 137-138°C.  $[\alpha]_{589}^{25} = 178^\circ$  (c = 0.00034).

(b) 3(S)-3-Allyl-1-cyclopropylmethyl-3-(3,4-dichlorophenyl)glutarimide

The above product (0.77 g, 2.59 mmol) was reacted with bromomethylcyclopropane (276  $\mu$ l 1.1 mol. equiv.) following the procedure of Preparation 5(c) to yield the 1-cyclopropylmethyl derivative (0.68 g). LRMS  $m/z = 352 (M+1)^+$ . TLC Rf 0.47 (silica, diethylether:hexane 1:1 by volume).

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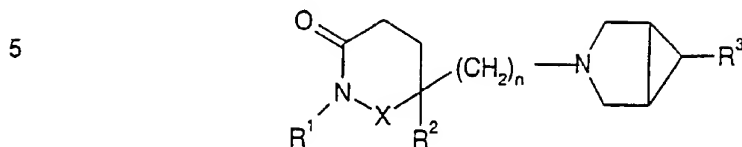
(c) 3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-formylmethyl-glutarimide

- Into a solution of the above compound (717 mg, 1.82 mmol) in methanol (40 ml) under nitrogen at -78°C was bubbled ozone at a rate of 50 ml/min (using a charge of 1.5A to generate ozone from oxygen) for twenty minutes. After this time the amperage was reduced to zero and oxygen bubbled through the reaction at a rate of 5 ml/min for ten minutes. The oxygen supply was then removed and a solution of dimethylsulphide (1.33 ml) in methanol (5 ml) was added dropwise and the reaction left to warm to room temperature for eighteen hours. The solvent was removed under reduced pressure and the reaction mixture partitioned between ethyl acetate (30 ml) and water (30 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure to give the title compound (630 mg) which was used without further purification. TLC R<sub>f</sub> = 0.18 (silica, diethyl ether:hexane 1:1 by volume). LRMS m/z = 354 (M+1).

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CLAIMS

1. A compound having the formula:



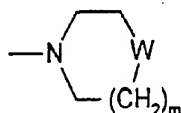
(I)

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkyl, aryl or aryl-(C<sub>1</sub>-C<sub>4</sub>)alkyl; wherein the C<sub>1</sub>-C<sub>6</sub> alkyl group is optionally substituted by one or more fluorine atoms and the C<sub>3</sub>-C<sub>7</sub> cycloalkyl or C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>4</sub>)alkyl group is optionally substituted in the cycloalkyl ring by up to two substituents each independently selected from halo, C<sub>1</sub>-C<sub>4</sub> alkoxy or halo(C<sub>1</sub>-C<sub>4</sub>)alkoxy;

R<sup>2</sup> is phenyl optionally substituted with one or two halo substituents or is indolyl, thienyl, benzothienyl, or naphthyl;

R<sup>3</sup> is NH<sub>2</sub>, -NR<sup>4</sup>SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl), -NR<sup>4</sup>SO<sub>2</sub> aryl, -NR<sup>4</sup>SO<sub>2</sub>N(R<sup>4</sup>)<sub>2</sub>,  
 20 -NR<sup>4</sup>CO(C<sub>1</sub>-C<sub>6</sub> alkyl), -NR<sup>4</sup>CO aryl or a group of the formula:



25 wherein W is O, NR<sup>5</sup>, CH(OH), CHCO<sub>2</sub>H, CHN(R<sup>4</sup>)<sub>2</sub>, CHF, CF<sub>2</sub>, C = O or CH<sub>2</sub>;

R<sup>4</sup> is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>5</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, C<sub>4</sub>-C<sub>8</sub> cycloalkanoyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>2</sub>-C<sub>6</sub>)alkanoyl, aryl CO-, C<sub>1</sub>-C<sub>6</sub> alkyl SO<sub>2</sub>-, (R<sup>4</sup>)<sub>2</sub>NSO<sub>2</sub>-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl SO<sub>2</sub>-, C<sub>3</sub>-C<sub>7</sub> cycloalkyl(C<sub>1</sub>-C<sub>6</sub>)alkyl SO<sub>2</sub>- or aryl SO<sub>2</sub>-;

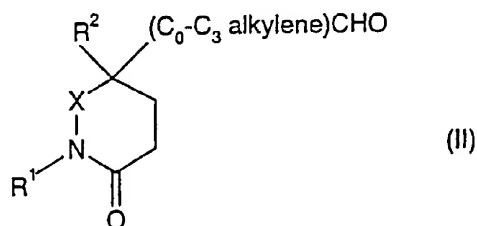
X is CH<sub>2</sub> or C = O;

m is 0, 1 or 2 with the proviso that m is not 0 when W is NR<sup>5</sup>, C=O, or O;  
 and n is an integer of from 1 to 4.

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2. A compound as claimed in claim 1 wherein X is CH<sub>2</sub> and R<sup>1</sup> is cyclopropylmethyl or benzyl.
3. A compound as claimed in claim 1 or claim 2 wherein R<sup>2</sup> is 3,4-
- 5 dichlorophenyl.
4. A compound as claimed in any one of claims 1 to 3 wherein n is 2.
5. A compound as claimed in any of claims 1 to 4 wherein R<sup>3</sup> is morpholino, methanesulphonylamino, pentafluorophenylsulphonyl, fluorophenylsulphonyl, or fluorophenylcarboxamido.
- 10 6. The compound 5(S)-5-(3,4-dichlorophenyl)-1-(cyclopropylmethyl)-5-(2-[1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ,6-morpholino-3-azabicyclo[3.1.0]hexane]ethyl)-2-piperidone.
7. A process for preparing a compound having the formula (I) as defined in claim 1 by reductive amination of a compound of the formula:

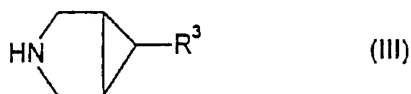
15



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where R<sup>1</sup>, R<sup>2</sup> and X are as previously defined for a compound of the formula (I),

25 and a compound of the formula:-



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or an acid addition salt thereof, where R<sup>3</sup> is as previously defined for a compound of the formula (I), in the presence of a reducing agent and optionally in the presence of an acid.



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8. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

5 9. The use of a compound of the formula (I), as claimed in any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof or pharmaceutical composition thereof for treating or preventing inflammatory diseases such as arthritis, psoriasis, asthma or inflammatory bowel disease; central nervous system disorders such as anxiety, depression, dementia or psychosis; gastro-intestinal disorders such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease; urogenital tract disorders such as incontinence or cystitis; pulmonary disorders such as chronic obstructive airways disease; allergies such as eczema, contact dermatitis or rhinitis; hypersensitivity disorders such as to poison ivy; peripheral neuropathies  
10 such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, burns, herpetic neuralgia or post-herpetic neuralgia; cough or acute or chronic pain.

15 10. A method of treatment of a human for treating or preventing inflammatory diseases such as arthritis, psoriasis, asthma or inflammatory bowel disease; central nervous system disorders such as anxiety, depression, dementia or psychosis; gastro-intestinal disorders such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease; urogenital tract disorders such as incontinence or cystitis; pulmonary disorders such as chronic obstructive airways disease; allergies such as eczema, contact dermatitis or rhinitis; hypersensitivity disorders such as to poison ivy;  
20 peripheral neuropathies such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, burns, herpetic neuralgia or post-herpetic neuralgia; cough or acute or chronic pain which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt thereof as  
25 claimed in any one of claims 1 to 6.

# INTERNATIONAL SEARCH REPORT

Int. Patent Application No.  
PCT/EP 96/05000

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D401/06 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 96 05193 A (PFIZER LTD ;PFIZER RES & DEV (IE); PFIZER (US); MACKENZIE ALEXANDE) 22 February 1996 cited in the application see the whole document ---	1-10
A	EP 0 512 901 A (SANOFI ELF) 11 November 1992 see abstract -----	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

3 February 1997

Date of mailing of the international search report

10.02.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

Kissler, B

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/05000

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body (Art. 52(4) EPC) the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/05000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9605193	22-02-96	AU-A- 3254995 BR-A- 9503582	07-03-96 30-04-96
EP-A-0512901	11-11-92	FR-A- 2676055 AU-B- 652046 AU-A- 1591692 CA-A- 2067877 FI-A- 951242 FI-A- 951243 JP-A- 5186425 NO-B- 178573 NZ-A- 242586 US-A- 5340822	06-11-92 11-08-94 05-11-92 04-11-92 16-03-95 16-03-95 27-07-93 15-01-96 26-10-95 23-08-94